REMARKS

Claims 2, 20-24, 38, 40 and 42-50 presently appear in this case. No claims have been allowed. The official action of September 22, 2006, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Claims 42 and 43 have been objected to as being essentially duplicates of claims 39 and 40, respectively. Appropriate correction has been required. This objection is respectively traversed, in part.

It appears that the examiner is correct that claims 39 and 42 were essential duplicates. Accordingly, claim 39 has now been deleted without prejudice. However, it is respectfully pointed out that claims 40 and 43 are not duplicates. Claim 40 does not provide that the protein must be a variant as described in claim 2, paragraph (B), having an amino acid sequence that is at least 95% identical with SEQ ID NO:3. It only states that the variant of (B) has 95% identity. Thus, the claim only further limits paragraph (B) of claim 2 but does not exclude the polypeptide of (A). Claim 40 still includes the protein of (A). On the other hand, claim 43 specifies that the protein consists of a variant of SEQ ID NO:3. Thus, a protein comprising the amino acid sequence of SEQ ID NO:3 as claimed on paragraph (A) of claim 2 would fall within the scope of claim 40. However, it would

not fall within the scope of claim 43. Claim 43 does not cover SEQ ID NO:3. Accordingly, claims 40 and 43 are not duplicates in view of the fact that it is possible for a protein to infringe claim 40 but not to infringe claim 43. Reconsideration and withdrawal of this part of the objection are therefore respectfully urged.

Claims 2, 20-24, 38-43 and 47-48 have been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The examiner states that the claims encompass any protein wherein at least a portion of the protein has 90% identity to SEQ ID NO:3, without providing any structural information with regard to sequences with 90% identity capable of binding to TRAF2. The examiner states that the description in the specification does not describe any variants of SEQ ID NO:3 of any kind that are capable of binding to TRAF2. Thus, the examiner considers the proteins to be defined by function only. The examiner states that there is no structural analysis of NAP to identify the relevant structural features that are required for binding activity. The examiner states that the skilled artisan cannot envision a sufficient number of embodiments of the instant invention from the instant specification because the specification only discloses a single protein. This rejection is respectfully traversed.

All of the rejected claims make clear that the variant must bind to TRAF2. Thus, the claims include the function of binding to TRAF2. Further, paragraph (B) of claim 2 states that the amino acid sequence of the variant is the same as the defined amino acid sequence of SEQ ID NO:3 except for changes to the sequence thereof that still leave at least 90% identity (claim 2) or 95% identity (claims 40 and 43), or that have only ten changes (claim 47) or only five changes (claim 48), or ten or five changes that are conservative changes (claims 49 and 50). Thus, the claims further define the sequences by structure.

The Guidelines for the Examination of Patent Applications under the 35 U.S.C. §112, paragraph 1, "Written Description" Requirement, as set forth in MPEP §2163, states at II.A.3.(a):

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. *Enzo Biochem,* [*Inc. v. Gen-Probe, Inc.*, 323 F.3d 956, 964, 63 USPQ2d 1609, 1613 (Fed. Cir. 2002)].

Here, the variant of claim 2(B) is defined by a complete or partial structure and other physical and/or chemical

properties. Binding is a physical property. There is effectively a partial structure because each variant must have at least 90% of the amino acid structure of the polypeptide defined in claim 2(A). Thus, this combination of partial structure and physical and/or chemical properties is sufficient to show that applicant was in possession of the claimed invention.

Binding alone is sufficient to establish the function of serving in affinity chromatography to isolate TRAF2. Note that the affinity chromatography function is mentioned, for example, at page 19, paragraph (i). Accordingly, the present claims fully satisfy the written description guidelines, as it is perfectly acceptable to show that one is in possession of a compound by identifying characteristics that include physical properties.

As to the question of whether or not the full scope of presently-claimed variants is supported by a sufficient written description in view of the fact that only a single species is disclosed in the specification, reference is made to the Revised Interim Written Description Guidelines Training Materials, also entitled "Synopsis of Application of Written Description Guidelines," (see www.uspto.gov/web/menu/written.pdf). Reference is particularly made to Example 14: "Product-by-Function," beginning on numbered page 53 of the Training Materials. In that

example, the specification exemplified a protein isolated from liver that catalyzed the reaction of A→B, which isolated protein was sequenced and was determined to have the sequence as set forth in SEQ ID NO:3. The specification also contemplated, but did not exemplify, variants of the protein wherein the variant can have any or all of the following: substitutions, deletions, insertions, and additions. The specification indicated that procedures for making proteins with substitutions, deletions, insertions, and additions are routine in the art and provided an assay for detecting the catalytic activity of the protein.

This description in the specification is very similar to the description that appears in the present specification. The present specification exemplifies a NAP protein that binds TRAF2. The sequence of this protein is specified. The specification contemplates, but does not exemplify, variants of the protein, with 90% or 95% identity or changes of 10, or 5 amino acid residues. The present specification also indicates that procedures for making such variants, including by modification of the DNA sequences encoding them, are routine in the art (see, for example, the first full paragraph on page 44) and provides an assay for determining whether any given protein binds to TRAF2. See, for example, the paragraph bridging pages 48 and 49.

In Example 14 of the Training Materials, the claim is directed to:

> A protein having SEQ ID NO:3 and variants thereof that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A→B.

The analysis in the Training Materials acknowledges that procedures for making variants of SEQ ID NO:3 are conventional in the art and that an assay is described which will identify other proteins having the claimed functionality. Moreover, procedures for making variants of SEQ ID NO:3 which have 95% identity to SEQ ID NO:3 and retain its activity were conceded as being conventional in the art. It would, of course, be understood that procedures for making variants of the polypeptide of SEQ ID NO:3, which variants are as defined in paragraph (B) of claim 2, are also conventional in the art.

The analysis goes on to point out that all variants of the claim must possess the specified catalytic activity and must have at least 95% identity to SEQ ID NO:3. Furthermore, because of the "having" language, the protein claimed may be larger than SEQ ID NO:3 or its variant with 95% identity to SEQ ID NO:3. The analysis points out that the specification contains a reduction to practice of the single disclosed species. The analysis concludes at pages 54-55:

> The specification indicates that the genus of proteins that must be variants of SEQ ID NO:3 does not have substantial variation since all the variants must possess the specified catalytic activity and must have at least 95% identity to the reference sequence, SEQ ID NO:3. The single species disclosed is representative of the genus because all members have at least 95%

> structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO:3 which are capable of the specified catalytic activity. One of skill in the art would conclude that applicant was in possession of the necessary common attributes possessed by the members of the genus.
>
> Conclusion: The disclosure meets the requirements of 35 USC §112, first paragraph, as providing adequate written description for the claimed invention.

Thus, it is apparent that if the single species disclosed is representative of the genus and an assay is present for identifying the members of the variants that are capable of the specified functionality, the written description requirement is met. Here, the requirement of 95% identity in claims 40 and 43 is exactly the same degree of identity as found to be acceptable in Example 14 of the Training Materials. For claims 47-50, the requirement of having no more than 10 changes (i.e., almost 99% identity or more), and the disclosure of the assay also are sufficient to identify all of the variants that are capable of the specified binding activity. As in the Training example, one of skill in the art would conclude applicants were in possession of the necessary common structure possessed by the members of the genus despite disclosure of only a single species.

While Example 14 of the Training Materials specifically relates to an example with 95% identity, the logic therein equally applies to variants with 90% identity. Accordingly, claim 2

should be considered to comply with the written description requirement for the same reasons that the written description Training Materials indicate that variants with 95% identity comply with the written description requirement.

As the Training Materials acknowledge that a genus of variants can be claimed based on the disclosure of only a single member of that genus, the situation in this case would warrant a similar analysis, whereby the variants defined in paragraph (B) of claim 2 (and even more so for the smaller sub-genera of claims 40, 43 and 47-50) must also be considered to be supported by the written description of the present specification. Reconsideration and withdrawal of this rejection is therefore respectfully urged.

Claims 2, 4 [*sic*, there is no claim 4], 20-24 and 38-43 have been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The examiner states that the test of enablement is whether one skilled in the art can make and use the claimed invention from the disclosures in the specification, coupled with information known in the art, without undue experimentation. The examiner states that as SEQ ID NO:3 is 949 amino acids in length, a protein having 90% or 95% identity to SEQ ID NO:3 would have up to 94 and 48 amino acids changed, respectively. The examiner states that such a 94 residue amino acid sequence can

represent an independently functioning domain, or a functional protein of its own. The examiner states that the instant application is claiming protein variants that have the functional ability to bind to TRAF2 based on homology alone. The examiner states that the disclosure does not indicate what sequences or domains of SEQ ID NO:3 are required for binding to TRAF2. The examiner states that the ability to identify protein sequences that bind to other protein sequences is not commensurate with the ability to make and use, which is the standard for meeting the enablement requirement. The examiner considers the invention to be highly unpredictable, thus requiring a good deal of trial and error experimentation in order to make and use the claimed invention. This rejection is respectfully traversed.

First of all, claim 2 has now been amended in order to clarify the scope of the present invention. Claim 2 provides that the protein is capable of binding to TRAF2. The protein comprises either a polypeptide consisting of the amino acid sequence of SEQ ID NO:3 or a variant consisting of an amino acid sequence that is at least 90% identical with SEQ ID NO:3, wherein the variant is capable of binding to TRAF2. While claim 2 is broad enough to read on fusion proteins with SEQ ID NO:3 or with a variant, it is clear that the variant itself must retain the ability to bind TRAF2 and that the

final protein must also maintain the capability of binding to TRAF2. It is, of course, an inherent property of SEQ ID NO:3 that it is capable of binding to TRAF2, as is clearly disclosed in the present specification.

As to the examiner's comments about the unpredictability of what sequence and structural requirements are necessary to bind to TRAF2, such arguments fail in view of the fact that it is not necessary to know in advance which variants of SEQ ID NO:3 would bind to TRAF2. The present specification at page 44 discloses standard procedures to prepare analogs, such as by conventional mutagenesis techniques on the DNA encoding the protein. Such mutagenesis techniques are well known to be able to induce approximate numbers of changes. Simple *in vitro* binding assays are described in the present specification. Indeed, simple binding assays can be done in a high throughput manner and do not involve undue experimentation.

The amount of experimentation that may be permitted in order to satisfy the enablement requirement of 35 U.S.C. §112 is discussed in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). In this regard, *Wands* states, 858 F.2d at 736-737, 8 USPQ2d at 1404:

> Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue

> experimentation. "The key word is 'undue,' not 'experimentation.'"
>
> > The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. Ansul Co. v. Uniroyal, Inc. [448 F.2d 872, 878-879; 169 USPQ 759, 762-763 (2d Cir. 1971), *cert. denied,* 404 U.S. 1018, 30 L. Ed. 2d 666, 92 S. Ct 680 (1972)]. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed***.
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> [Footnotes omitted - the latter quote being from *In re Jackson,* 217 USPQ 804, 807 (Bd. App. 1982)]

Wands goes on to state, 858 F.2d at 737, 8 USPQ2d at 1404:

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman* [230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986)]. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. [Footnotes omitted]

In analyzing these factors in this case, the conclusion must be reached that the experimentation is not undue. As to the first factor, the quantity of

experimentation may be significant, as random mutations would have to be generated and screening conducted of the encoded proteins using a simple binding assay. However, in the *Wands* case, it was found that routine screening does not necessarily amount to undue experimentation.

With respect to the second factor, the amount of guidance or direction presented, the present specification refers at pages 31 and 39 to the Sambrook reference, which is the laboratory manual used by everyone of ordinary skill in this art. Everything in it is known and within the skill of those of ordinary skill in the art. Less guidance is needed for well-known techniques. Guidance as to a specific binding screen is provided, for example, at page 19.

As to the third factor, the presence or absence of working examples, the binding assay at page 19 is sufficiently detailed to serve as a working example.

As to the fourth factor, the nature of the invention, the nature of the invention is such that substantial experimentation is acceptable. As will be discussed in the following factors, the field of this invention requires a very high level of skill in the art, and practitioners are well inured to screening that takes substantial experimentation quantitatively.

As to the fifth factor, the state of the prior art, random mutagenesis and binding assays are all well-documented in the prior art. The examiner has not doubted this fact, and so it has not been necessary to submit evidence proving it. The present invention does not involve any of these specific techniques *per se*. Their use on the novel protein sequences of the present invention is the advance made by the present inventors.

As to the sixth factor, the relative skill of those in the art, those of ordinary skill in the art of recombinant DNA technology is very high, usually requiring a Ph.D. and/or substantial laboratory experience. For such persons, a greater amount of experimentation would be considered to be routine than for technologies requiring a lower level of skill in the art.

As to the seventh factor, the predictability of the art, predictability is not relevant here, as no predictability is necessary. One need only do the experiments and screen; the results will provide all of the answers. It is not necessary to predict the answers in advance.

As to the eighth factor, the breadth of the claims, paragraph (B) of claim 2 is not so broad so as to require undue experimentation to find what would fall within it for

the reasons as discussed above with respect to all of the other factors.

Accordingly, as in *In re Wands*, analysis of the facts of the present case, considering the factors enumerated in *Ex parte Forman*, leads to the conclusion that undue experimentation would not be required to practice the invention. There was a high level of skill in the art at the time when the application was filed and all of the methods needed to practice the invention were well known.

As to the examiner's argument that the claims could read on a protein in which the N-terminal 94 residues are completely different from those of SEQ ID NO:3, which sequence could represent an independently functioning domain, this is a far-fetched argument. 90% of the binding polypeptide is the same as SEQ ID NO:3, which is the TRAF-binding protein. Any variant that maintains 90% identity and which is found to bind to TRAF2, would be expected to bind to TRAF2 for the same reason that SEQ ID NO:3 binds to TRAF2. The examiner has not met his burden of suggesting any 94 amino acid sequences that would be known to bind to TRAF2 and that do not appear in SEQ ID NO:3. Certainly, the examiner has not met this burden for a 48 amino sequence as in claims 40 and 43. In any event, this argument does not really relate to enablement.

The examiner has repeated several times that the enablement standard requires that the skilled artisan be able to make the invention and that making the invention and identifying the invention are not synonymous. This statement is not correct, however, as any variant that binds to TRAF2 is the present invention. Once one has identified variants of SEQ ID NO:3 that will bind to TRAF2 one must necessarily know how to make and use it. Once it is identified, it has already been made. As the specification teaches that one prepares such proteins recombinantly, one must have in hand a clone that produces the protein in order to test the protein for binding. Furthermore, as long as the protein binds to TRAF2, it can be used in the present invention as that is the only requirement for use of the protein. The protein can be used in affinity chromatography to purify TRAF2. Thus, identifying a variant that bind to TRAF2 necessarily allows one to make and use the claimed invention.

The examiner states that applicant is claiming protein variants that have the functional ability to bind to TRAF2 based on homology alone. However, as indicated above, applicant recognizes the need to screen such variants for capability of binding to TRAF2. Thus it is not necessary to predict binding by homology but one can determine binding by routine mass screening. This does not amount to undue

experimentation for the same reasons as discussed by the court in *In re Wands*.

For all of these reasons, reconsideration and withdrawal of this rejection are respectfully urged.

It is noted that the examiner has withdrawn all of the art rejections and has indicated that claims 3 and 44-46 contain allowable subject matter.

It is submitted that all the claims now present in the case clearly define over the references of record and fully comply with 35 U.S.C. 112. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant(s)

By /rlb/
Roger L. Browdy
Registration No. 25,618

RLB;jmd
Telephone No.: (202) 628-5197
Facsimile No.: (202) 737-3528
G:\BN\I\inl2\wallach25\Pto\2007-02-22Amd.doc